

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

| | | | | | | |
|---|--|----|---|-----|----|-------------------------------------|
| To: | | | | | | |
| ROCHE DIAGNOSTICS GMBH Patent Department D-68298 Mannheim ALLEMAGNE | | | | | | |
| K | Roche Diagnostics GmbH Patentabteilung | | | AB | | |
| JG | | | | HIL | | |
| SI | 26. Juni 2000 | | | WN | | |
| Kn | | | | PA | | |
| P | KÖ | KL | S | SZ | IM | Date of mailing (day/month/year) |
| | | | | | WB | 16.06.2000 |

**NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**
(PCT Rule 71.1)

| | | | |
|--|---|---|--|
| Applicant's or agent's file reference <u>5217/OB/WO-Koe</u> | IMPORTANT NOTIFICATION | | |
| International application No. <u>PCT/EP99/02361</u> | International filing date (day/month/year) <u>07/04/1999</u> | Priority date (day/month/year) <u>07/04/1998</u> | |
| Applicant <u>ROCHE DIAGNOSTICS GMBH et al.</u> | | | |

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office
 D-80298 Munich

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Authorized officer

Vullo, C

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PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

| | | |
|--|---|---|
| Applicant's or agent's file reference 5217/OB/WO-Koe | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/EP99/02361 | International filing date (day/month/year) 07/04/1999 | Priority date (day/month/year) 07/04/1998 |
| International Patent Classification (IPC) or national classification and IPC C07K14/00 | | |
| <p>Applicant ROCHE DIAGNOSTICS GMBH et al.</p> <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application | | |
| Date of submission of the demand 03/08/1999 | Date of completion of this report 16.06.2000 | |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Vollbach, S Telephone No. +49 89 2399 8715 | |



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/02361

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-19 as originally filed

Claims, No.:

1-24 as originally filed

2. The amendments have resulted in the cancellation of:

- the description, pages:
 the claims, Nos.:
 the drawings, sheets:

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | |
|-------------------------------|----------------------|
| Novelty (N) | Yes: Claims 1-24 |
| | No: Claims |
| Inventive step (IS) | Yes: Claims |
| | No: Claims 1-24 |
| Industrial applicability (IA) | Yes: Claims 1-24 |
| | No: Claims |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/02361

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/02361

1. In the present communication the following documents are referred to:

D1: EP-A-0 784 984

D2: JUVVADI, PADMAJA ET AL: 'Synthetic Melittin, Its Enantio, Retro, and Retroenantio Isomers, and Selected Chimeric Analogs: Their Antibacterial, Hemolytic, and Lipid Bilayer Action' J. AM. CHEM. SOC. (1996), 118(38), 8989-8997, 1996, XP002116435

D1 discloses the production of dioleoylmelittin and its ability to form complexes with DNA. The complexes mediate efficient transfection of various cell types.

D2 is concerned with the preparation of retro melittin and with the finding that said retro melittin retains its antibacterial activity while the toxic effect against eucaryotic cells is abolished. Thus it has been shown that the two distinct functions inherent to melittin can be separated by preparing the retro type of melittin.

2. D1 is considered to represent the closest prior art. The difference of the claimed subject-matter vis à vis D1 consists of the usage of the retro-melittin whereas the latter applies the melittin. Thus the technical problem underlying the alleged invention consists in the provision of an improved dioleoylmelittin which is less toxic to the eucaryotic cell.

The above difference, however, cannot be regarded to substantiate an inventive step for the claimed subject-matter. This also apply with respect to the comparative data between the compound of D1 and those of the present application provided by the applicant. There was no doubt that the compounds of the present application are superior over those described in D1. However, the improvement is obvious with regard to D2. The reason is that a person skilled in the art being confronted with the above problem would certainly contemplate to use the retro-melittin because this analog is described to promote electrical conductivity in lipid bilayer, to possess high antimicrobial activity while having lost its hemolytic activity. These properties are exactly those required for the production of a compound useful for efficient gene delivery.

Furthermore, also the application of an additional helper lipid and/or short chain phospholipid, cationic lipid as claimed in present claim 10 is obvious from the disclosure of D1. For the reasons given above none of the claims fulfil the requirements of Article 33(2) PCT.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/02361

3. For the assessment of the present claims 14-24 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
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| Applicant's or agent's file reference 5217/0B/W0 | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/EP 99/ 02361 | International filing date (day/month/year) 07/04/1999 | (Earliest) Priority Date (day/month/year) 07/04/1998 |
| Applicant ROCHE DIAGNOSTICS GMBH et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
 - contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. **Certain claims were found unsearchable (See Box I).**

3. **Unity of invention is lacking (see Box II).**

4. With regard to the **title**,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

PCT/EP 99/02361

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 14-24
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 14-24
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claim 1 is formulated ambiguously, the definition of claim R3: " a basic, membrane disturbing peptide with a reversed amide backbone " is obscure, and does not properly define a structural feature characterizing the desired peptide residue.

The use of these property/paramater in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the property/parameter the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely compounds recited in the examples and claims, closely related compounds and the general idea underlying the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/02361

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07K14/00 A61K47/48 A61K9/127

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | EP 0 784 984 A (HOFFMANN LA ROCHE) 23 July 1997 (1997-07-23) cited in the application the whole document --- | 1-4 |
| Y | | 1-24 |
| X | LEGENDRE J Y: "Dioleoylmellitin as a Novel Serum- Insensitive Reagent for Efficient Transfection of Mammalian Cells" BIOCONJUGATE CHEMISTRY, vol. 8, 1 January 1997 (1997-01-01), pages 57-63, XP002088445 ISSN: 1043-1802 cited in the application the whole document --- | 1-4 |
| Y | | 1-24 |
| | | -/- |

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

24 September 1999

Date of mailing of the international search report

03/11/1999

Name and mailing address of the ISA

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Authorized officer

Veronese, A

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/02361

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X | JUVVADI, PADMAJA ET AL: "Synthetic Melittin, Its Enantio, Retro, and Retroenantio Isomers, and Selected Chimeric Analogs: Their Antibacterial, Hemolytic, and Lipid Bilayer Action" J. AM. CHEM. SOC. (1996), 118(38), 8989-8997 ,1996, XP002116435 * See Retroenantiomellitin * figure 1; table 1 --- | 8,9 |
| Y | DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US SCHLAEGER, E.-J. ET AL: "Synergistic enhancement of transient expression by dioleoyl -melittin (DOM) and polyethylenimine (PEI) in mammalian cells in suspension culture" retrieved from STN Database accession no. 130:61776 XP002116436 abstract & NEW DEV. NEW APPL. ANIM. CELL TECHNOL., PROC. ESACT MEET., 15TH (1998), MEETING DATE 1997, 117-120. EDITOR(S): MERTEN, OTTO-WILHELM; PERRIN, PIERRE; GRIFFITHS, BRYAN. PUBLISHER: KLUWER, DORDRECHT, NETH. , | 1-24 |
| A | DEMPSEY C E: "The Actions of Mellitin on Membranes" BIOCHIMICA ET BIOPHYSICA ACTA. MR. REVIEWS ON BIOMEMBRANES, vol. 1031, 1 January 1990 (1990-01-01), pages 143-161, XP002088446 ISSN: 0304-4157 the whole document --- | 1-24 |
| A | LEGENDRE J Y ET AL: "Short-Chain Phospholipids Enhance Amphipatic Peptide-Mediated Gene Transfer" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 217, no. 1, 5 December 1995 (1995-12-05), pages 179-185, XP002088443 ISSN: 0006-291X the whole document ----- | 1-24 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/02361

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|-----------|------------------|
| EP 0784984 | A 23-07-1997 | BR | 9700703 A | 01-09-1998 |
| | | CA | 2195169 A | 18-07-1997 |
| | | JP | 9202799 A | 05-08-1997 |
| | | TR | 9700035 A | 21-08-1997 |